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| 09/741,106 | 12/21/2000 | Michael A. Innis | 12441.00003 | 7590 |

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| EXAMINER |
|---|
| KAM, CHIH MIN |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | 13 |

DATE MAILED: 05/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/741,106 | INNIS ET AL. | |
| | Examiner | Art Unit | |
| | Chih-Min Kam | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11,13-27,73 and 88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14 and 15* is/are allowed.

6)☒ Claim(s) *1-11,13,16-27,73 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of the Claims*

1. Claims 1-11, 13-27, 73 and 88 are pending.

Applicants' amendment filed on February 27, 2003 (Paper No. 12) is acknowledged, and applicants' response has been fully considered. Claims 1, 2, 14, 15 and 16 have been amended, claim 12, 28-72 and 74-87 have been cancelled, and a new claim 88 has been added. As indicated in the previous Office Action, all proteins ((a)-(h)) in claims 8 and 22, all sequences ((a)-(i)) in claims 9 and 23; and all sequences ((a)-(k)) in claim 15 are included for examination. Thus, claims 1-11, 13-27, 73 and 88, and all the sequences cited in the claims are examined.

### ***Objection Withdrawn***

2. The previous objection of the specification, regarding the use of brackets ([..]), is withdrawn in view of applicants' response at page 10 in Paper No. 12.

3. The previous objection of claims 10, 11, 17-18, 24 and 25, regarding the use of brackets ([..]), is withdrawn in view of these claims which have not been amended, and applicants' response at page 10, and in Paper No. 12.

### ***Rejection Withdrawn***

### *Claim Rejections-Obviousness Type Double Patenting*

4. The previous rejection of claim 12, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U. S. Patent 6,174,721 or U. S. Patent 5,589,359, is withdrawn in view of applicants' cancellation of the claim in Paper No. 12.

***Claim Rejections - 35 USC § 112***

5. The previous rejection of claims 2-16, under 35 U.S.C.112, second paragraph, regarding the claim not further limiting claim 1, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicants' response at pages 11-12 in Paper No. 12.

***Claim Rejections - 35 USC § 102***

6. The previous rejection of claim 2 under 35 U.S.C. 102(b) as being anticipated by Voet *et al.* (Biochemistry (text book), page 59-63 (1990)), is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 15-16 in Paper No. 12.

***Claim Objections***

7. Claim 2 is objected to because the amended claim cites "wherein A, B, C, D, E, F, G may comprise portions of native TFPI or TFPI-2 sequences", which does not include the term "or non-native sequence" that has been cited in the original claim, but the deletion of the term has not been shown in the Marked copy.

8. Claim 16 is objected to because of the use of [...] in the amended claim. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. For example, applicant has used "[$X_1$-B-$X_2$]" in such a manner that appears that the instant brackets would indicate deleted material and is thus, confusing as to whether chimeric protein would include "$X_1$-B-$X_2$" or not. The applicant can only amend by cancellation and presentation of a new claim. See also changes to 37 CFR 1.121 in Amendment rules package (Final Rule

published on 8 Sep. 2000 (65 Fed. Reg. 54603), see also O. G. of 19 Sep. 2000 (1238 Off. Gaz. Pat. Office 77)).

***Claim Rejections-Obviousness Type Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-11, 16-25 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U. S. Patent 6,174,721.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11, 16-25 and 73 in the instant application disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. This is obvious in view of claims 1-17 in the patent which disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1 of TFPI-2 and a Kunitz-type domain 2 of TFPI, wherein chimeric protein lacks sites for N-glycosylation. Both sets of claims cite a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-

type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. Thus, claims 1-11, 16-25 and 73 in present application and claims 1-17 in the patent are obvious variations of a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI.

10. Claims 1-11, 16-27 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U. S. Patent 5,589,359.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11, 16-27 and 73 in the instant application disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. This is obvious in view of claims 1-24 in the patent which disclose a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. Both sets of claims cite a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. Thus, claims 1-11, 16-27 and 73 in present application and claims 1-24 in the patent are obvious variations of a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI.

In response, applicants indicate they will consider filing a Terminal Disclaimer upon indication of allowability of the pending claims.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-11, 13, 16-27, 73 and 88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or, a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFP or a mutein thereof, where the substitution in the mutein is defined (page 8, line 19-page 9, line 3; page 10, line 5-12), and the chimeric protein containing the mutein retains the inhibitory activity toward factor VIIa/TF complex and factor Xa, does not reasonably provide enablement for a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or, a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFP or a mutein thereof, where the mutation in the mutein is not defined, and the inhibitory activity of the chimeric protein containing the mutein toward factor VIIa/TF complex and factor Xa is not known. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-11, 13, 16-27, 73 and 88 encompass a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein

thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. The specification indicates the mutein of TFPI or TFPI-2 has 1-5 amino acid substitutions in the wild-type sequence, and further describes certain substitutions in the muteins, however, it does not identify most substitutions in the TFPI or TFPI-2 nor demonstrates the effect of the substitution on the affinity for factor VIIa/TF and factor Xa (page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21; page 10, lines 5-12). There are no indicia that the present application enables the full scope in view of the chimeric protein comprising the muteins of TFPI or TFPI-2 as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the claims are enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the scope of the claims, the state of the prior art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the muteins of TFPI or TFPI-2 in the chimeric protein, which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

The specification has shown the mutein has the amino acid sequence of SEQ ID NO:9 (276 amino acid residues) or SEQ ID NO:19 (161 amino acid residues), where a Lys at position 36 is substituted with Arg. There are no other working examples indicating the claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (WO 91/02753) indicates TFPI with certain amino acid residues such as C-terminal region deleted has TFPI activity but with no or low heparin binding activity, however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the muteins and the effects of the chimeric proteins containing the muteins to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof, and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or a Kunitz-type domain 1 of TFPI-2 or a mutein thereof, and a Kunitz-type domain 2 of TFPI or a mutein thereof. The specification indicates muteins have 1-5 amino acid substitutions in the wild-type sequence, and describes certain substitutions in the muteins (e.g., the substitution at the P1 reactive site and substitutions at positions within 5 amino acids of the P1 reactive sites in Kunitz-type domains; page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21), however, it does not identify most substitutions in the TFPI or TFPI-2, nor demonstrates the effect of the substitution on the affinity for factor VIIa/TF and factor Xa. Moreover, there are no working examples indicating various muteins except for the substitution at P1 reactive site of Kunitz-type domains, e.g., SEQ ID NO:9. Furthermore, the specification has not demonstrated the chimeric proteins containing various muteins of Kunitz-type domain 1 or 2 of TFPI or TFPI-2 have inhibitory activity against factor VIIa/TF and factor Xa. Since the specification fails to provide sufficient teachings on identities of various muteins and the effects of the chimeric proteins containing the muteins, it is necessary to have additional guidance on the muteins and to carry

out further experimentation to make/use chimeric proteins containing the muteins, and assess the inhibitory effects to Factor VIIa/TF/Xa.

(5). Predictability or unpredictability of the art:

As indicated in the previous sections, the specification only demonstrates the substitution at the P1 reactive site such as in SEQ ID NO:9 or 19, it does not identify various substitutions in muteins of TFPI and TFPI-2. Since the claims encompass numerous unidentified variants, the effects of the chimeric proteins containing various muteins of TFPI and TFPI-2 are unpredictable.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not identified these variants nor indicated the effects of the chimeric proteins containing these variants. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the inhibitory effect of the claimed invention toward Factor VII/TF/Xa.

In response, applicants indicate the chimeric protein in claim 1 comprises a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFPI or a mutein thereof, or, a Kunitz-type domain 2 of TFPI-2 or a mutein thereof and a Kunitz-type domain 1 of TFPI or a mutein thereof, and claims 2-13 are dependent from claim 1, thus the chimeric protein in claims 2-13 precludes the combination of A=B=C=0 and a=b=0. The argument is persuasive,

thus the rejection regarding this matter is withdrawn. Regarding the specification does not enable the chimeric proteins containing various muteins of the recited Kunitz domain, applicants indicate the specification teaches numerous examples of TFPI and TFPI-2 muteins (page 8, line 19-page 9, line 3; page 10-lines 5-12), and the amino acid sequences of Kunitz domains, N-linked glycosylation sites, and TFPI and TFPI-2 were known in the art, and the specification also teaches how to make the disclosed muteins (page 9, line22 to page 10, line 4), thus one skilled in the art would be able to make and use chimertic muteins of Kunitz-type domain 1 or 2 of TFPI or TFPI-2 without undue experimentation. The argument is not found persuasive because the mutein cited in the claim does not have any structural or function description, thus, the claim would include various muteins, not just those indicated in the specification, thus it requires further guidance on the identities of the muteins and further experimentation to assess the inhibitory effects of the chimeric proteins containing these muteins against Factor VIIa/TF/Xa.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 2-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-13 are indefinite because of the use of the term "wherein a, b are integers from 0-6" or "wherein A, B, C, D, E, F, G may comprise portions of native TFPI or TFPI-2 sequences". The term "wherein a, b are integers from 0-6" or "wherein A, B, C, D, E, F, G may comprise portions of native TFPI or TFPI-2 sequences" renders the claim indefinite, it is unclear

how a compound in generic formula A-$(X_1)_a$-B-$(X_2)_b$-C with a=0 or b=0 can be a chimeric protein comprising a Kunitz domain of TFPI-2 and a Kunitz domain of TFPI? It is also unclear whether A, B, C, D, E, F or G comprises portions of native TFPI or TFPI-2 sequences as to "may comprise", and which portions of native TFPI or TFPI-2 sequences are intended. Claims 3-13 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

In response, applicants indicate the chimeric protein in claim 1 comprises a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFPI or a mutein thereof, or, a Kunitz-type domain 2 of TFPI-2 or a mutein thereof and a Kunitz-type domain 1 of TFPI or a mutein thereof, and claims 2-13 are dependent from claim 1, thus the chimeric protein in claims 2-13 precludes the combination of A=B=C=0 and a=b=0 (page 11 of the response). The argument is persuasive, thus the rejection regarding this matter is withdrawn, however, if a or b is 0, the chimeric protein having the structure of A-$(X_1)_a$-B-$(X_2)_b$-C would not contain a Kunitz domain of TFPI-2 and a Kunitz domain of TFPI as required by claim 1, thus the citation of a or b being 0 does not conform the limitation set forth in claim 1. Regarding the term "wherein A, B, C, D, E, F, G may comprise portions of native TFPI or TFPI-2 sequences", applicants indicate the recitation is open to inclusion of any native TFPI or TFPI-2 sequences or any sequences that are not part of a native TFPI or TFPI-2 sequences, as indicated in the section above, it is not clear which part of TFPI or TFPI-2 sequences are included in the chimeric protein, and what sequences are non-native TFPI or TFPI-2 sequences.

***Conclusion***

13. Claims 1-11, 13, 16-27, 73 and 88 are rejected, it appears claims 14 and 15 are free of prior art and allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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April 27, 2003

Christopher S.F. Low
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